October 2017

The Value of Active Pharmaceutical Ingredients

How is a pharmaceutical specialty developed?

- **The development of a new pharmaceutical specialty is a long and costly process.** It can last up to ten years and involves several phases: The preclinical phase (also known as phase 0), three additional phases of clinical experimentation on an increasingly larger number of subjects, followed by a fourth Phase of "post marketing surveillance" or pharmaco-vigilance.

- In order to produce a single medicinal product, **several hundred or sometimes thousand molecules are subjected to preliminary laboratory tests** where a first selection is made. During this **preclinical phase**, the selected molecules are subjected to a pharmacological screening consisting of a series of in vitro tests - to identify the therapeutic activity - as well as in vivo tests on laboratory animals in order to understand their pharmacokinetic and pharmacodynamic properties. Subsequent tests of increasing complexity will allow the **selection of the molecules that will be active ingredients suited to human use to verify safety and tolerability (clinical phase 1).**

- In practice, **an active ingredient** must demonstrate its therapeutic activity, have an acceptable administration route, be absorbed once administered – or be effective where required - reach its target(s), perform its action and be subsequently eliminated.
    - **At the end of this selection process, only a few molecules remain that can proceed to Clinical Phases 1, 2 and 3** (start of human clinical trials), subject to prior authorisation by the competent national bodies, most likely the Ministry of Health. Typically the company will take care to patent these molecules prior to submitting the necessary documentation in order to obtain this authorisation.

How is an Active Pharmaceutical Ingredient produced?

- **The Active Pharmaceutical Ingredient (API)** is the biologically active constituent of the drug, **responsible for the curative activity** that one expects when taking a medicine. It must therefore be produced according to **Good Manufacturing Practices** (GMP) defined by regulatory authorities and binding on the legislative level.

- For an API producer, working according to GMP entails being able to obtain a license to manufacture, following an inspection by the national regulatory agencies, certifying that

the company works in accordance with the requirements of the EU legislation on GMP. It entails operating in a plant which has the adequately trained personnel, premises and equipment for the production and the conservation of each and every product, as well as the quality systems and processes that guarantee the proper functioning of the equipment and **the consistency and quality** of the APIs produced. **This guarantees that the company is able to provide products that continuously meet the high quality standards required**.

- The production of Active Ingredients requires a significant technological contribution from the API manufacturer who must develop a new chemical process in order to improve **industrial efficiency**. It is therefore crucial for the API manufacturer to have a **cutting-edge Research & Development (R&D) facility**, thus enabling the transition from laboratory scale to pilot plant and then to full industrial scale, whilst maintaining the characteristics required by the pharmaceutical industry for the production of the drug and its commercial distribution.

- In this phase, important investments on equipment and production facilities are required from the API manufacturer in order to **optimize production efficiency and yield.**

- In Europe GMP is governed by EU law. Furthermore strict environmental, health and safety (ESH) standards are required to operate manufacturing plants. Based on these regulations "gold standards" are applied to meet excellence in industrial safety, environmental protection and health & safety at work. The development of **increasingly "clean" technologies** is an important prevention measure of environmental impacts and accidental events.

- **GMP standards** require from manufacturers, inter alia, the validation[i] of their equipment, processes, analytical methods and cleaning methods

- At the expiry of its patent the active ingredient can be used for the **production of generic drugs**, allowing access to healthcare to a wider population as well as allowing the National Health Services to enhance their expenditure.

[i] i.e. documentary evidence to demonstrate that a procedure, process, or activity carried out in testing and then production maintains the desired level of compliance at all stages